Immunology & Rheumatology

Opsonisation

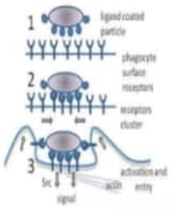
OPSONIZATION

The process whereby opsonins make an invading microorganism more susceptible to phagocytosis

OPSONIN

An antibody or complement protein that enhances phagocytosis by marking an antigen is called opsonin

- Major opsonins are
1. Immunoglobulin (Ig)G antibodies
2. Certain plasma lectin → MANNOSE BINDING LECTIN
3. C3b and it's cleavage products e.g. iC3b (inactive C3b)



- It is a process by which a particulate antigen becomes more susceptible to phagocytosis.
- Opsonic index is defined as ratio of phagocytic activity of the patient's blood for a given bacterium to that of a normal individual.
- Phagocytic index is the average number of phagocytosed bacteria per polymorphonuclear leukocytes from stained blood films.
- Phagocytic index denotes the phagocytic activity of blood and thus helps in measuring opsonic index.

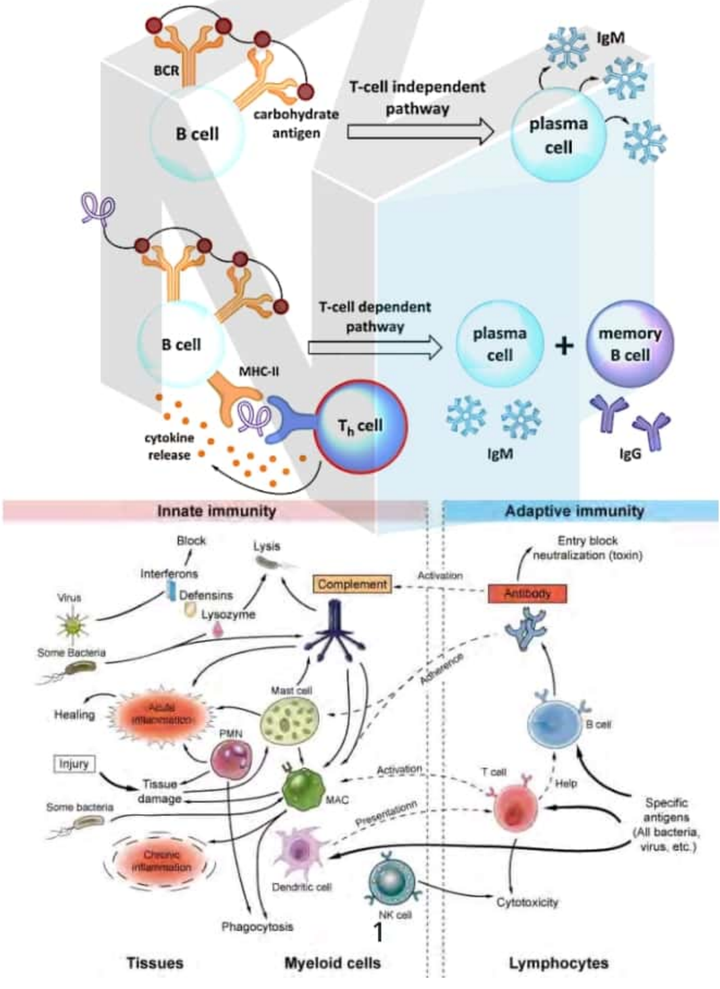
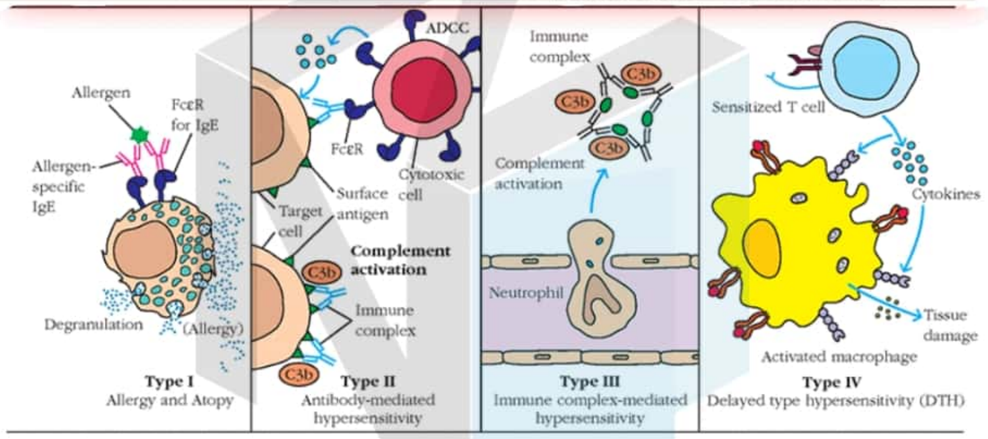


TABLE 16.1: Features of various types of hypersensitivity reactions

	Type I	Type II	Type III	Type IV
Immune response altered	Humoral	Humoral	Humoral	Cell mediated
Immediate or delayed	Immediate	Immediate	Immediate	Delayed
Duration between appearance of symptoms and antigen contact	2 to 30 minutes	5–8 hour	2–8 hours	24–72 hours
Antigen	Soluble	Cell surface bound	Soluble	Soluble or bound
Mediator	IgE	IgG	Ag-Ab complex	T_{DTH} cell
Effector mechanism	Mast cell degranulation	• ADCC • Complement-mediated cytolysis	Complement activation and inflammatory response	Macrophage activation leads to phagocytosis or cell cytotoxicity
Desensitization to the allergen	Easy, but short lasting	Easy, but short lasting	Easy, but short lasting	Difficult, but sustained
Typical manifestations	• Anaphylaxis • Asthma • Atopic dermatitis	• Transfusion reactions • Rh incompatibility • Hemolytic anemia	• Arthus reaction • Serum sickness • Glomerulonephritis • Rheumatoid arthritis	• Tuberculin test • Granuloma formation in tuberculosis, leprosy, etc • Contact dermatitis



Immunodeficiency Disorders

1) Deficiency of Phagocytes

Leucocyte adhesion deficiency

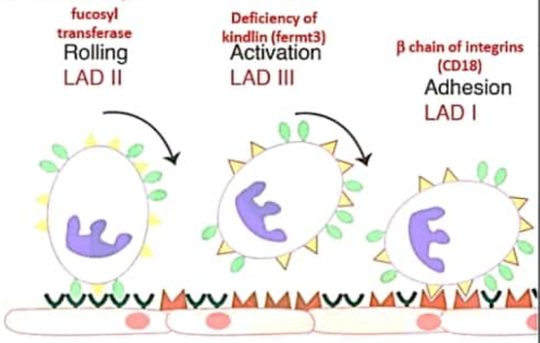
Omphalitis
No abscess
Extreme neutrophilia

LAD I – deficiency of β chain of integrins (CD18)

LAD II – deficiency of fucosyl transferase

LAD III – deficiency of kindlin (fermt3) – no activation of integrin

LAD I > LAD III > LAD II



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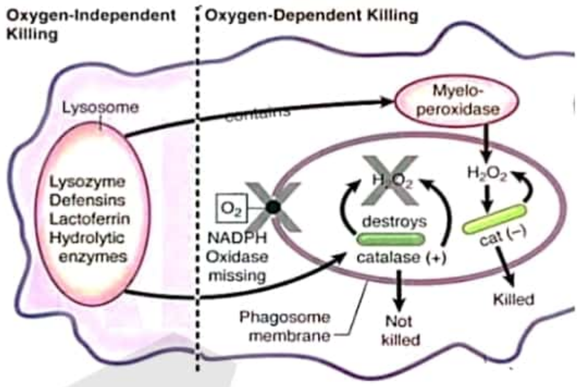
Chronic granulomatous disease

Deficiency of NADPH oxidase

Recurrent infections with catalase + ve organisms

Nitroblue tetrazolium dye reduction test – ve



Chediak Higashi Syndrome

Mutation in **LYST** (regulates lysosomal trafficking) - Defective fusion of phagosome & lysosome

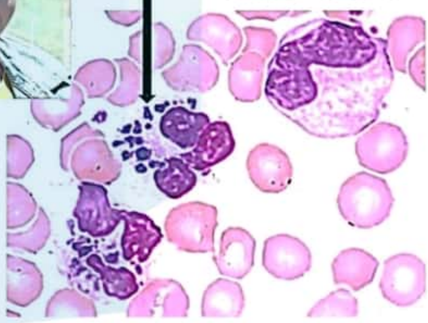
Abnormal melanocytes – albinism (lack of skin & eye pigment)

Abnormal platelet – bleeding disorders

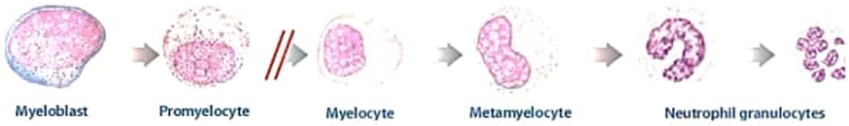
Abnormalities in nerve cells

Aggressive but non malignant infiltration of organs by lymphoid cells

Giant lysosome in phagocytes – cannot kill bacteria



Severe Congenital Neutropenia (SCN)



Defect in granulopoiesis at promyelocytic stage (Bone Marrow)

ELANE mutation (MC)– neutrophil elastase defect

Autosomal dominant (MC)

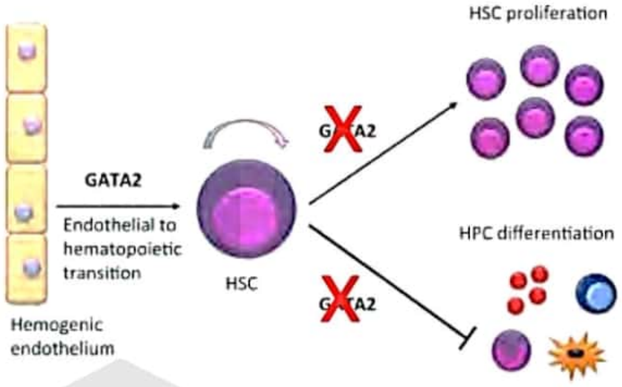
Bacterial infections at interface between the body & external milieu (orifices, wounds, respiratory tract)

GATA2 deficiency

GATA2 – transcription factor for hematopoiesis

Monocytopenia with NTM infections (Mono-MAC)

Myelodysplasia, AML



2) T Cell Deficiencies

SCID (severe combined immunodeficiency)

Mutation in Cytokine receptor (IL2Rγ) - X-linked

JAK3 deficiency (AR)
(↓Signaling pathway – No maturation of cells)

Adenosine deaminase (ADA) deficiency (AR) – accumulation of deoxyadenosine – inhibits ribonucleotide reductase– prevents DNA synthesis

Rag1 or rag 2 gene mutation (AR)
Impairment of VDJ recombination

Di George Syndrome

Congenital heart defects
Abnormal facies
Thymus – absent
Cleft palate
Hypocalcemia

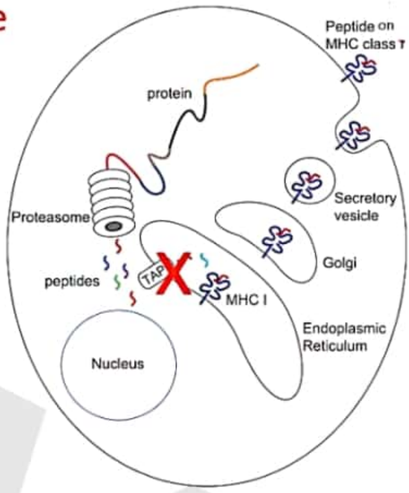
CATCH 22

Chromosome 4 **22q11**

Bare lymphocytic syndrome

Defect in TAP - ↓MHC I expression

Granulomatous lesions in mid face



Hyper IgE syndrome
(Job or Buckley syndrome)

FATE of Job (Biblical figure)

F – Facies (coarse or leonine facies)

A – Abscess (cold staphylococcal abscess)

T – Teeth (Retained primary teeth)

E – Eczyma

Deficiency of TH17 cells

Waiter serving Wiskott Aldrich's Whiskey

Defect in WASP gene affecting T cells

When you drink whiskey

Your blood **E**thyl **A**lcohol goes **up**

↑IgE & ↑IgA

And **M**ental function goes **down**

↓IgM

W - Wiskott

A - Aldrich

I - Immunodeficiency

T - Thrombocytopenia

E - Eczyma

R – Recurrent bacterial infections

Ataxia-telangiectasia

DACOIT in **ATM** at **11** PM

ATM – gene mutation (chr 11) – defect in DNA repair (e.g. after radiation theray)

D – Dysarthria
A – Ataxia
C – Cancers (leukemia & lymphoma)
O – Ocular apraxia
I – Involuntary movement (chorea, athetosis, dystonia, myoclonic jerks)
T – Telangiectasia

A= ↓IgA - Sinopulmonary infections
↑AFP

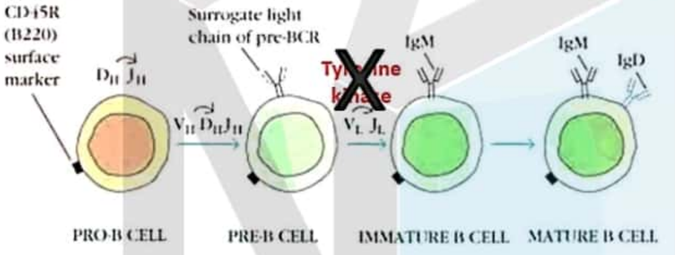
Zeta chain associated protein (ZAP) deficiency
defective signals from TCR

Nezelof syndrome
AR, thymus hypoplasia

Purine Nucleoside phosphorylase deficiency
AR (chr 14)
PNP catalyses guanine to hypoxanthine
Elevated deoxy-GTP levels – T cell toxicity

3) B Cell Deficiencies

Bruton agammaglobulinemia



Mutation in BTK gene – deficiency of tyrosine kinase – total absence of B cells – No Ig
X-linked
Pre B cells in bone marrow

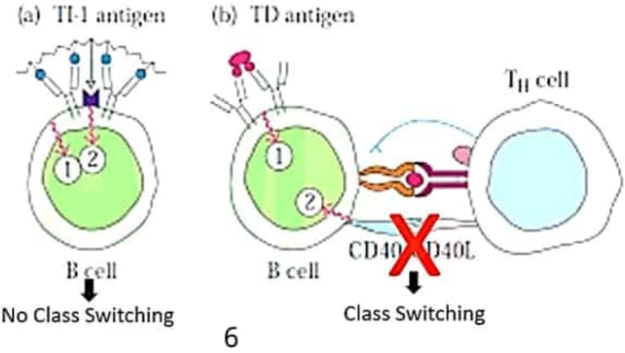
Hyper IgM syndrome

Mutation in CD40L gene in T cells (X-linked)

No class switching

↑ IgM

Recurrent infections specially respiratory tract



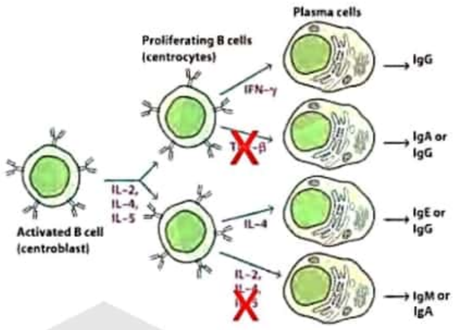
Selective IgA deficiency

↓ T cell cytokine (TGFβ & IL5) – differentiates B cells to plasma cells for IgA secretion

Defective mucosal immunity – recurrent sinopulmonary infections

MC primary immunodeficiency

No passive immunisation



Common variable hypo γ globulinemia

Normal B cells

Defect to differentiate to plasma cells

Onset – 2nd or 3rd decade

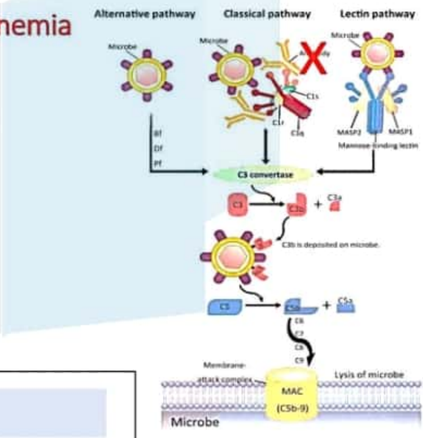
Transient hypo γ globulinemia of infancy

Abnormal delay in the initiation of synthesis of IgG (IgA or IgM sometimes)

Defect in complement activation & opsonisation

Resolves by 18 to 24 months

Normal response to vaccine

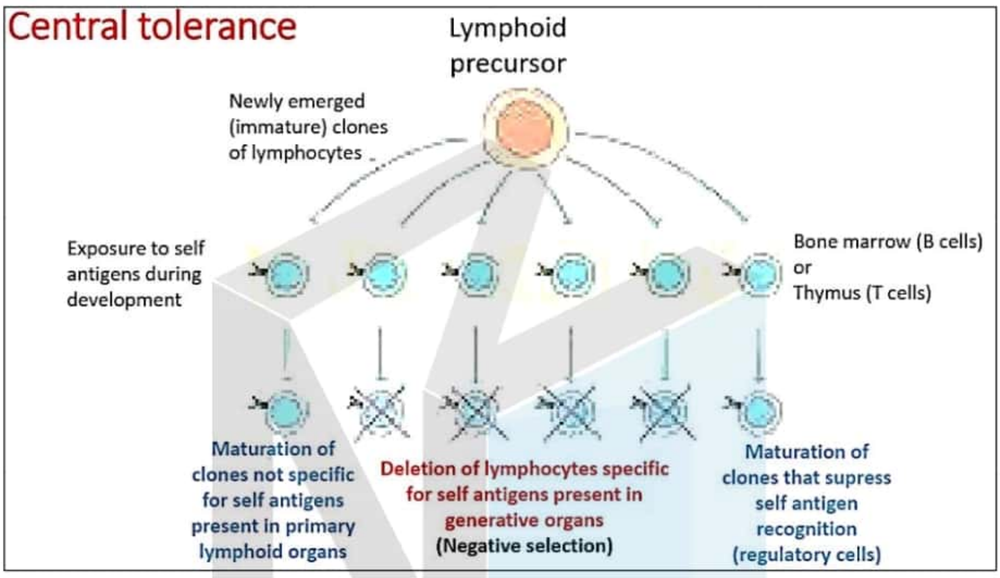


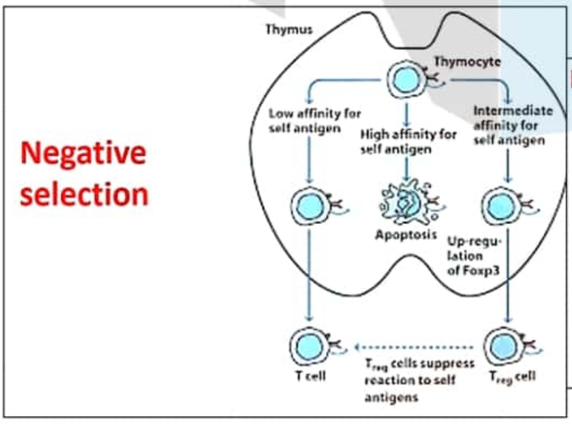
Classification

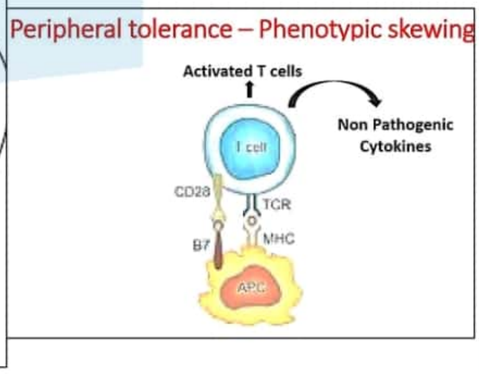
T cell disorders	B cell defects
-Severe combined immunodeficiency -Wiskott aldrich syndrome(Xp11) -Ataxia telengectiasia(11q) -Digeorge anomaly	-XL agammaglobulinemia -Common variable immunodeficiency -Selective IgA deficiency -AR agammaglobulinemia -Hyper-IgM syndromes- XL
Phagocyte disorders	**Complement disorders**
-Chronic granulomatous disease -Leukocyte adhesion defect -Chediac higashi syndrome -Myeloperoxidase deficiency -Cyclic neutropenia (elastase defect)	-C1q deficiency -Factor I deficiency -Factor H deficiency -Factor D deficiency -Properdin deficiency

Autoimmunity

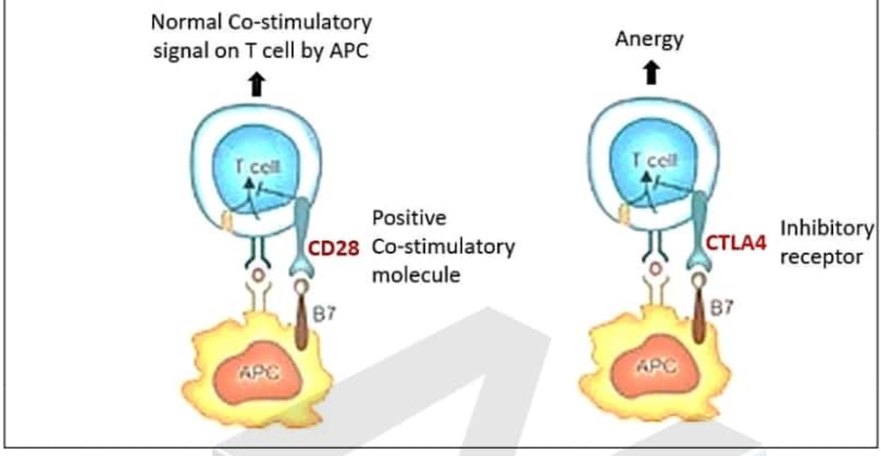
- Concept by Paul Ehrlich
- Autoimmunity- "horror autotoxicus"
- Body's own immunocompetent cells or antibodies act against self antigens
- Prevented by- Immunological tolerance


Central tolerance
Lymphoid precursor
Newly emerged (immature) clones of lymphocytes
Exposure to self antigens during development
Bone marrow (B cells) or Thymus (T cells)
Maturation of clones not specific for self antigens present in primary lymphoid organs
Deletion of lymphocytes specific for self antigens present in generative organs (Negative selection)
Maturation of clones that supress self antigen recognition (regulatory cells)



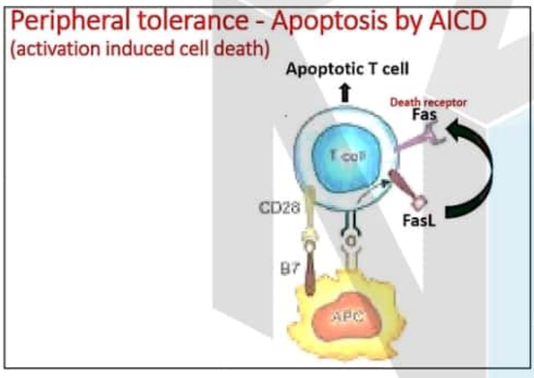


Peripheral tolerance - Anergy

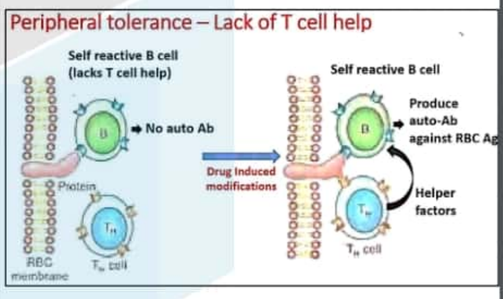


Peripheral tolerance - Apoptosis by AICD

(activation induced cell death)



Peripheral tolerance – Lack of T cell help



Mechanisms of autoimmunity

Breakdown of one or more mechanisms of immunological tolerance

- Breakdown of T cell Anergy
- Loss of T_{reg} cells
- Failure of AICD (activation induced cell death)
- Release of sequestered antigens
- Molecular mimicry
- Polyclonal lymphocytic activation (superantigen)
- Exposure to Cryptic Self-epitopes

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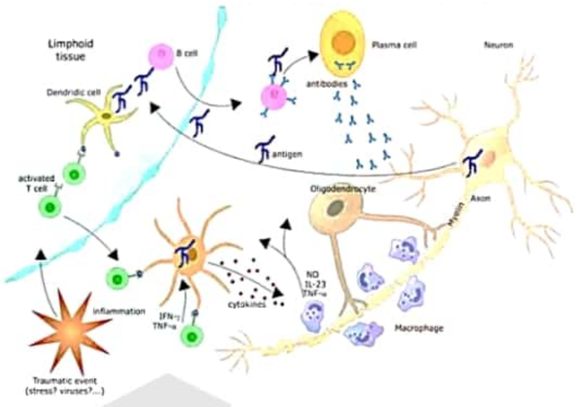
Multiple sclerosis

Breakdown of T cell anergy
T cells react to *m*yelin *b*asic *p*rotein (MBP) or *p*roteo*l*ipid *p*rotein (PLP) – both components of the myelin sheaths surrounding neurons in the CNS

Loss of T_{reg} cells

Release of sequestered Ag
*m*yelin *b*asic *p*rotein (MBP)

Type III hypersensitivity



Systemic lupus erythematosus

Autoantibodies to DNA, histones, RBC, platelets, leukocytes & clotting factors

⬇

Immune complex

⬇

Activates complement cascade

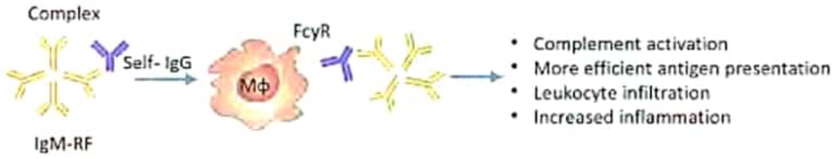
Type III hypersensitivity

Rheumatoid arthritis

Autoantibodies (Rheumatoid factors "IgM") binds to normal circulating IgG

⬇

Immune Complex



- Complement activation
- More efficient antigen presentation
- Leukocyte infiltration
- Increased inflammation

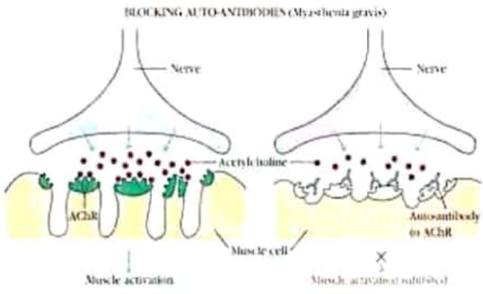
Type III hypersensitivity

Myasthenia gravis

Binding of auto-antibodies to the acetylcholine receptor (AChR)

blocks the normal binding of acetylcholine & subsequent muscle activation

Type II hypersensitivity (Non cytotoxic)

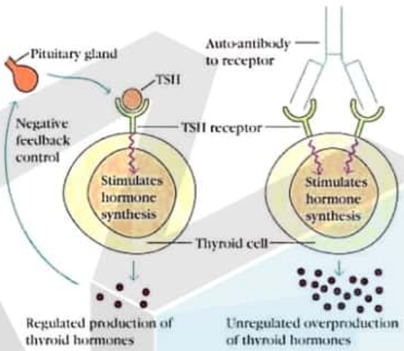


Graves disease

Binding of auto-antibodies to the TSH receptor

stimulates unregulated overproduction of thyroid hormones

Type II hypersensitivity (Non cytotoxic)



Rheumatology

- Immune excess disorders
- Suspect in case of unexplained, recurrent febrile episodes
- In India, Infection is the First Differential, especially TB
- Can mimic Immune excess disorders
- HIGH INDEX OF SUSPICION RECOMMENDED!
- Since symptoms are non-specific:
  - FOCUS IS ON LABARATORY TESTING FOR AUTO-IMMUNE DISEASE
  - THE MOST SENSITIVE ANTIBODY AND HENCE THE PREFFERED
  - SCREENING TEST FOR AUTO-IMMUNE DISEASE IS "ANA" TESTING

Rheumatology Disorders: 3 groups

Based on the following:	LUPUS group	ARTHRITIS group	VASCULITIS group
Characteristic feature, if present	Wolf-bite like skin rash	Joint deformity	Purpuric skin rash
Screening Antibody present	Anti-Nuclear Antibody (ANA)	Rheumatoid factor (RAF)	Anti-Neutrophilic cytoplasmic antibody (ANCA)

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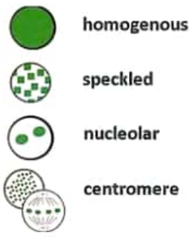
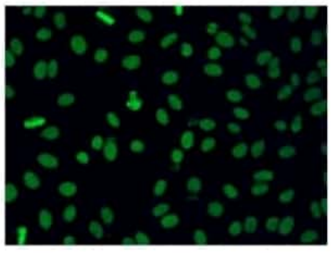
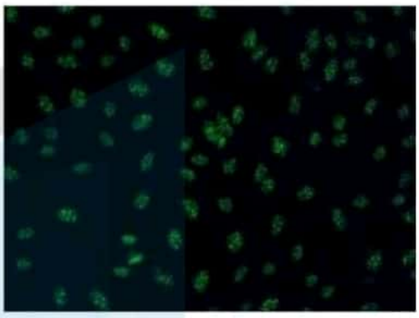
ANA Immunofluorescence patterns:



1. **Homogenous Pattern**
   - Corresponds to both : Anti-dsDNA & Anti-Histone Ab
   - Most common pattern in SLE



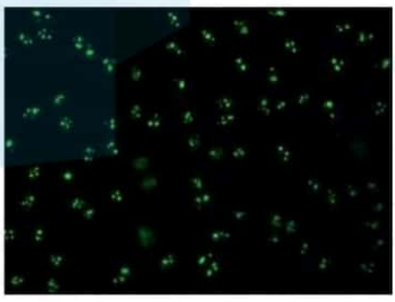
2. **Centromere Pattern**



Corresponds to :
Anti-Centromere antibody

Probable Diagnosis :
CREST syn/Limited SSc

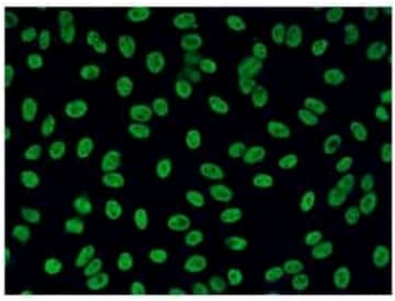
3. **Nucleolar pattern**



Corresponds to Anti-SCL-70
(Anti-topoisomerase 1 Ab)

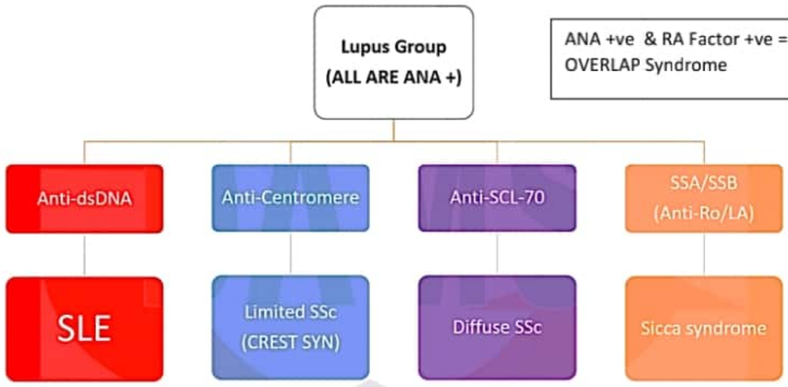
Probable Diagnosis :
Diffuse SSC
(Systemic Sclerosis)

4. **Speckled Pattern**



Corresponds to :
SSA/SSB(Anti-Ro/La)/
Anti-U1-RNP

Probable Diagnosis :
Sicca syndrome/MCTD



1. Acute : Malar rash

Erythematous Macular rash over the maxillary area sparing the nasolabial fold is most characteristic of SLE.

2. Chronic : Discoid rash

Fibrotic, painless papulonodular rash seen over the scalp, face and the neck area.

Clinical Feature: SYNOVITIS (Most Common, but Non-Specific) –

Non-Erosive Arthritis **[Jaccoud's Arthritis]**

Can mimic Swan -Neck deformity of RA

Most Specific C/F : Skin Rash

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SLE DIAGNOSIS

- SLICC Criteria (≥4 present)
- **NEW SCORING SYSTEM FOR SLE DIAGNOSIS**

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

If absent, do not classify as SLE
If present, apply additive criteria

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

Total score:

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

DCT IS NO LONGER PART OF DIAGNOSTIC CRITERIA
ANA Negative patient can NEVER be SLE

Skin Manifestations of SYSTEMIC SCLEROSIS

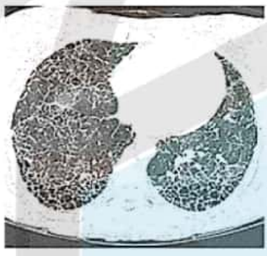
- Raynaud's Phenomenon (M/C)
  - Both in Limited & Diffused Systemic Sclerosis

- Edema (Early onset)
  - Non-specific

- Shortening of the fingers
  - Most Specific symptom
  - Late Onset

Dx: 70% Idiopathic → Always do ANA to include/confirm autoimmune disorders (AID)

MC in RA: UIP



MC in AID: NSIP

UIP: Multiple spaces- honeycombing with involvement of the subpleural area.

NSIP: Basal Ground glass opacity with subpleural sparing and is steroid responsive

Approach to Inflammatory Arthritis

- **Pauci-arthritis** (< 5 joints)
  - **Mono-arthritis**: Trauma, Septic, Gout
  - **Oligo-arthritis**: Pseudo-Gout
- **Poly-arthritis** (>= 5 joints)
  - **Axial-dominant**
  - **Appendicular dominant**

2: Check dominant joints

- **Axial-dominant** (Spine affected)
  - **Ankylosing Spondylosis (AS)**
    - Male dominant arthropathy
    - 90% : HLA-B27 association
    - MC affects : Sacro-iliac joint leading to Low Back Pain.
    - 70% : Arthritis is preceded by Recurrent unilateral uveitis
- **Appendicular-dominant** (Peripheral joints)
  - **Symmetrical** with Predominant Small Joint involvement
  - **Asymmetrical** with Predominant Large Joint involvement

AS is always B/L

All SpA are associated with HLA-B27

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3: based on the pattern involved

Symmetrical with Predominant Small Joint involvement

- **RA : Predom. Articular features** — MC cause: Inflamm. Polyarthritis
- **Psoariatic arthropathy (PsA) :** can mimic RA due to pattern

Asymmetrical with Predominant Large Joint involvement

- **IBD-associated arthropathy**
- **Reactive arthritis (ReA)**

Inflammatory Polyarthritis

RHEUMATOID ARTHRITIS	SPONDYLOARTHROPATHY
• RA Factor Positive (Seropositive)	• RA Factor Negative (Seronegative)
• HLA-DR4/DRB1 (Sporadic)	• HLA-B27 (Strong Family H/O)
• Axial involvement : Rare	• Axial : Relatively common
• Predom. feature : Articular	• Extra-articular predominant
• 1st line Rx : DMARDS	• 1st line Rx : NSAIDS

Psoariatic Arthropathy

- Joint involvement can mimic RA
- Skin/Nail changes Preceded the joint involvement in majority
- In 5-10%, arthritis precedes.
- Early DIP involvement differentiates from RA.

ONCHOLYSIS (NAIL PEELING)

IBD-associated arthropathy

- Asymmetrical Large Joints.
- May affect UL joints (viz. Shoulders, Elbow)
- Most commonly preceded by diarrhea.
- Associated with CD >> UC

Pyoderma gangrenosum

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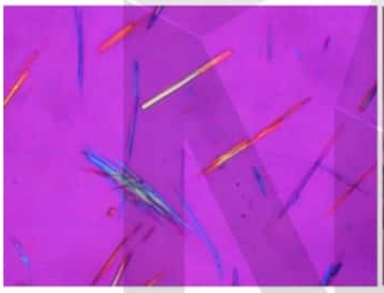
REACTIVE ARTHRITIS

- Asymmetrical Large Joints. Predominantly affects weight bearing joints i.e. LL joints.
- **Most commonly preceded by:**

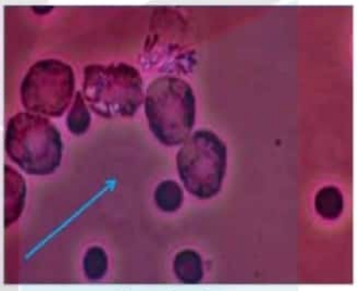
Chlamydia (Urine Infection)

Others : Salmonella, Shigella, Campylobacter associated diarrhea

Keratoderma Blenorrhagia

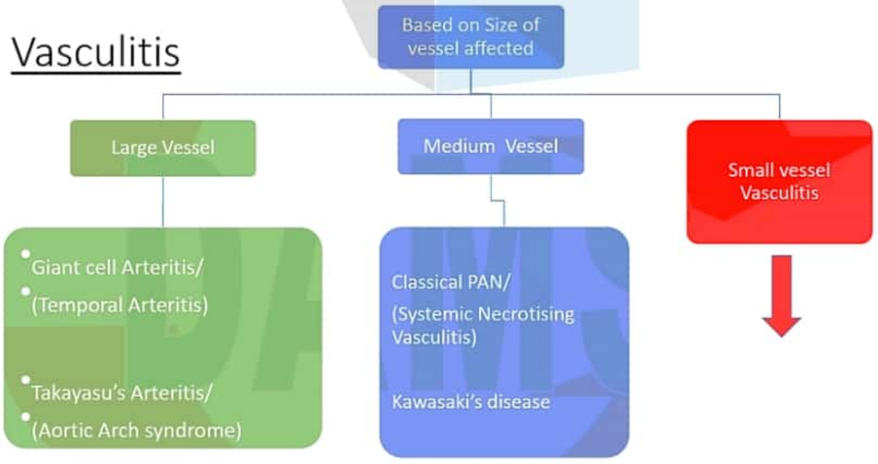


GOUT
Needle Shaped crytsal



Pseudo-Gout
Rhomboid shaped crystal

Vasculitis



Takayasu is aka Pulseless disease

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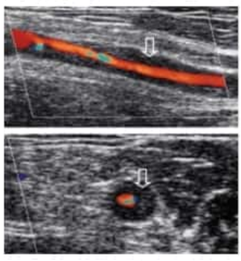
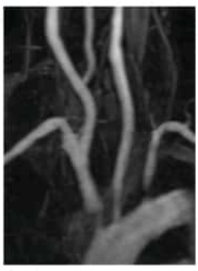
Giant cell Arteritis

Gold Standard- Temporal Artery Biopsy (but Non sensitive)

Beneficial Ix: USG Doppler- Thickening of the vessel wall also known as the HALO sign





Takayasu's Arteritis

MRI Angiography: vessel wall thickening & enhancement, stenosis of the coronary ostia, coronary arterial aneurysms, combination of stenosis and aneurysms ('string of pearls sign')

Polyarteritis Nodosa

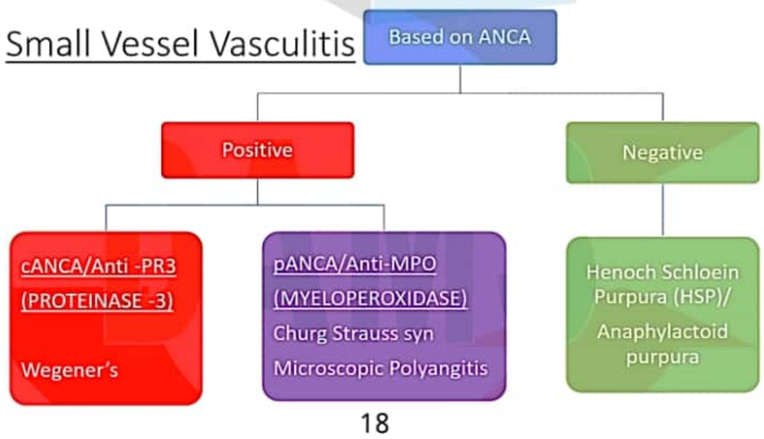
Unique pathology: Immune complex mediated disease causing Fibrinoid necrosis at the bifurcation of the Medium Sized arteries and thus the microaneurysm formation

Ix: Renal Angiography → Microaneurysms can been seen

Kawasaki's Disease

M/C manifestation – Non Exudative conjunctivitis

Can cause: Cardiac Death in children



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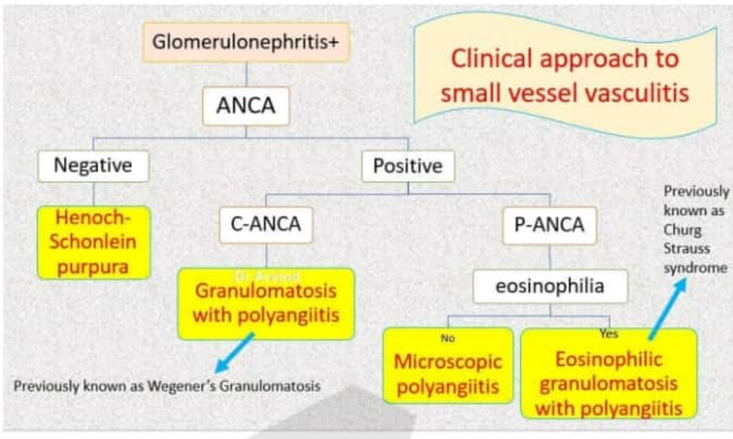

Bechet's Disease = Variable Vessel Vasculitis (Small+ Medium + Large)

- Painful Oral Ulcers- Essential Criteria
- Also Presence of one or more of the minor criteria:
  - Erythema nodosum (also seen in Sarcoidosis)
  - Sterile Hypopyon formation (can lead to blindness)